Remarks/Arguments

This application claims methods for preparing one or more compounds via combinatorial biosynthesis. Specifically, the claimed methods comprise providing one or more starter units that are substrates for one or more modular biosynthetic enzymatic machinery systems. Examples of modular biosynthetic enzymatic machinery systems include fatty acid synthase, polyketide synthase, peptide synthetase or terpene synthase (page 5, line 32 to page 6, line 5 of the specification). The type of starter unit selected is dependent on the modular biosynthetic enzymatic machinery system used (page 7, lines 20-22 of the specification). For example, if peptide synthetase is selected as the modular biosynthetic enzymatic machinery system, starter units are amino acid derivatives (page 7, lines 24-25 of the specification). Whereas, when a polyketide synthase is used as the modular biosynthetic enzymatic machinery system, thioesters derivatives are used as starting materials (page 7, lines 12-14 of the specification and Figs. 1 and 2, Example 3).

One or more of the starter units includes a functional handle that is reacted with a functionality present on a solid support to form one or more support bound starter unit. For example, the starter unit can include, or be modified to include, an alkyne (page 8, lines 20-25 of the specification and Fig. 3), which can be coupled to a solid support that has an alkyne functional group via a Glaser Coupling reaction (page 9, lines 16-22 of the specification). The support bound starter units are provided to one or more modular biosynthetic enzymatic machinery systems to generate a collection of template structures which are functionalized with synthetic organic chemistry. This collection may be provided to the modular biosynthetic enzymatic machinery system and functionalized with synthetic organic chemistry one or more times until the desired support bound collection of structures is generated.

Rejections of Claims 1-3 and 5-23 under 35 U.S.C. § 112, First Paragraph for Lack of Written Description

Pending claims 1-3 and -23 stand rejected for lack of written description. In particular, the Examiner states that the disclosure in the specification does not reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. This rejection is respectfully traversed; reconsideration and withdrawal is

requested.

The written description requirement imposes a duty on patent applicants to notify the public of the scope and content of their inventions. The requirement is satisfied if one skilled in the art would reasonably conclude that the inventors were in possession of the claimed invention at the time the patent application was filed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). See also Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 4, 1099 (2001). A determination of whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by those skilled in the art at the time that the application was filed. *In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996).

Number of Methods/Number of Compounds

The Examiner asserts that Applicant is claiming "virtually an infinite number of methods for producing virtually an infinite number of compounds." The Examiner bases this assertion on several lines of reasoning. First, the Examiner contends that Applicant provides no structural limitations for the starter units, handles and solid supports used in conjunction with the claimed methods. Second, the Examiner contends that the claimed biosynthetic enzymatic machinery includes an unknown number of enzymes and/or enzymatic machinery system constituents. Third, the Examiner contends that no limitations are provided for the synthetic organic chemistry that is further used to diversity the biosynthetic products. Applicant addresses each of these lines of reasoning in turn.

First, Applicant disagrees with the Examiner's assertion that Applicant provides no structural limitations for the starter units, handles and solid supports. The Examiner asserts that because no structural limitations have been placed on the starter units, handles and/or solid phase resins, the variation in the genus of claimed methods would be enormous. However, claim 1, step (c), explicitly recites that the provided starter units are provided to one or more biosynthetic enzymatic machinery systems *in vitro*, "wherein the biosynthetic enzymatic machinery system is selected from the group consisting of natural and modified polyketide synthases, natural and modified peptide synthetases, natural and modified terpene synthases, and natural and modified animal fatty acid synthases..." Substrates for each of these biosynthetic enzymatic machinery systems (i.e., starter units) are known to those skilled in the art. Applicant has disclosed

exemplary starter units for polyketide synthases, terpene synthases, and peptide synthases (see page 7, lines 8-14 and lines 22-25). Compatible starter units that act as substrates for these and other recited biosynthetic enzymatic machinery systems are well within the knowledge of those skilled in the art. Thus, the recitation of particular biosynthetic enzymatic machinery systems limits the universe of potential starter units significantly, i.e., to those starter units that are substrates for the recited biosynthetic enzymatic machinery systems.

Similarly, regarding the recited handles and solid supports, Applicant does in fact provide structural limitations for these elements. Applicant has disclosed properties that a solid support should have to be useful in the claimed methods. For example, the specification states that solid supports should have a functional group that can bind to a handle on a starter unit, such as an alkyne, olefin or iodoalkene (page 8, lines 14-26). Applicant discloses Glaser coupling, olefin metathesis and Stille Coupling reactions for coupling alkynes, olefins and iodoalkenes to solid supports that have one or more alkyne or olefin groups (see page 9, lines 16-29). Furthermore, Applicant provides specific guidance as to the number of handles that should be used based on the structural complexity of the starter unit and the specific biosynthetic enzymatic machinery system(s) that are used (see page 8, line 26 – page 9, line 15).

Thus, the Examiner is incorrect in asserting that Applicant provides no structural limitations for the starter units, handles and solid supports used in conjunction with the claimed methods. The described limitations on the possible starter units, handles and solid supports that may be used restricts the variation in the genus of claimed methods such that one skilled in the art would understand, based on the disclosure, that Applicant was in possession of the claimed invention at the time of filing.

Second, Applicant asserts that the Examiner's contention that the claimed biosynthetic enzymatic machinery includes an unknown number of enzymes and/or enzymatic machinery system constituents misses the point of the written description analysis. Claim 1 recites a method for combinatorial biosynthesis of one or more compounds comprising subjecting one or more starter units to one or more biosynthetic enzymatic machinery systems. Applicant has previously amended claim 1 to recite that the biosynthetic enzymatic machinery system(s) are selected from a limited number of particular systems. The relevant question is not whether each and every family member of each recited biosynthetic enzymatic machinery system is disclosed. Rather, the relevant question is whether one skilled in the art would understand from the

specification that the inventors were in possession of the claimed invention at the time of filing. That is, would a person skilled in the art have understood that the inventors were in possession of the recited biosynthetic enzymatic machinery systems? The answer to this question is clearly "yes".

Whether any particular enzyme falls within one of the recited families is easily determined by one skilled in the art. One skilled in the art would be able to easily identify family members of any of the recited biosynthetic enzymatic machinery systems based on any number of factors including structural and/or sequence identity or similarity to known members of each family, conservation of the catalytic core and whether the enzyme in question is functionally similar in that it catalyzes the reaction common to the family. Furthermore, Applicant has disclosed in the specification that researchers have made various modifications to certain preferred biosynthetic enzymes that alter their catalytic properties, indicating that those skilled in the art are not only able to generally identify family members of a given biosynthetic enzymatic machinery system, but are in fact able to specifically engineer altered versions of these enzymes (see page 6, lines 8-19).

Third, Applicant asserts that the Examiner is incorrect in the assertion that no limitations are provided for the synthetic organic chemistry that is further used to diversity the biosynthetic products. On page 14, lines 14-27, Applicants disclose that template structures can be functionalized using nucleophilic addition, functionalization of hydroxyl groups with electrophiles, Buchwald-Hartwig aminations, Heck coupling, Stille coupling, Sonogashira/Catro-Stephens coupling, Suzuki coupling, carbonylations, Mitsunobu reaction, hydroacylation, azide cycloaddition, nitrone cycloaddition, and nitrile oxide cycloaddition.

Again, the relevant question is whether one skilled in the art would understand from the specification that the inventors were in possession of the claimed invention. Each of these exemplary functionalization reactions disclosed (as well as other standard functionalization reactions) is known to those skilled in the art. One skilled in the art would be able to choose which functionalization reaction or reactions to employ in a given combinatorial biosynthesis based on the starter units provided and the biosynthetic enzymatic machinery systems utilized (see page 15, lines 1-4: "A skilled artisan in the field of synthetic organic chemistry will be able to readily identify those reagents capable of reacting to create further diversity at selected sites in the inventive template structures and starter units to generate compounds and libraries of

compounds reminiscent of natural products.") Indeed, in order to practice the invention as claimed, the practitioner is limited to those functionalization reactions that are capable of acting on the product of the combinatorial biosynthesis product. As such, the universe of potential synthetic organic chemistry reactions that may be used on any given combinatorial biosynthesis product is limited.

Working Examples

The Examiner further asserts that the specification does not adequately describe the claimed methods because the inventors have provided a working example of the methods. The Examiner argues that "the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed." As an abstract principle, Applicant of course does not disagree with this assertion. However, whether a given disclosure provides adequate written description is a fact-intensive inquiry. As held in *In re Alton*, whether the specification provides adequate description must be determined by examining the disclosure in light of the knowledge possessed by one skilled in the art at the time the application was filed. 76 F.3d 1168 (Fed. Cir. 1996). Thus, although the general level of skill in the art cannot provide the required description, the description provided must be read from the point of view of one skilled in the art.

Applicant submits that it was well within the knowledge and capability of one skilled in the art at the time the application was filed to subject a given substrate, *which substrate is initially chosen by the practitioner*, to an appropriate biosynthetic enzyme. Applicant discloses several enzyme/substrate combinations merely as examples of possible enzyme/substrate combinations (see page 7, lines 20-32). Applicant has not asserted that any particular enzyme/substrate combination or combinations is a critical feature of the claimed invention. In fact such an assertion would undermine important aspects of the present application, which is directed generally towards combinatorial methods useful in the synthesis of "one or more" compounds. Rather, methods of the invention encompass the concept that diverse compounds can be synthesized using a combination of enzymatic reactions and organic chemistry. Those skilled in the art are well versed in appropriate enzyme/substrate combinations, particularly those specific enzymes recited in claim 1. Furthermore, those skilled in the art are capable of identifying those functionalization reactions that are appropriate for any given product produced

by the enzymatic reaction. Thus, the description of methods for the combinatorial biosynthesis of one or more compounds comprising both enzymatic reactions and organic chemistry reactions must be read from the point of view of one skilled in the art, that is, from the point of view of those who are already knowledgeable about specific enzymatic and/or organic chemistry techniques.

As the Examiner is surely aware, disclosure of working examples of techniques known to those skilled in the art is not necessary. *See, e.g., Manual of Patent Examination Procedure*, ch. 2164.05(a), discussing this issue in the context of enablement. *See also In re Buchner* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and is available to the public.") Applicant submits that the guidance required by the written description requirement is provided in the disclosure of novel methods of synthesizing compounds using both enzymatic reactions and organic chemistry.

Screening Step

Finally, the Examiner argues that Applicant does not claim a screening step in order to "allow a person of skill in the art to sort through an find a 'useful' compound and/or library from the large number of compounds that would unquestionably result from the claimed method." In support of this argument, the Examiner cites *University of Rochester v. G.D. Searle & Co, Inc.* 358 F.3d 916, 60 USPQ2d 1886 (Fed. Cir. 2004). The Examiner correctly notes that in *Rochester*, claims reciting "a method for selectively inhibiting PGHS-2 enzymatic activity comprising administering a non-steriodal compound that selectively inhibits activity of the PGHS-2 gene" failed to meet the written description requirement because the patent neither disclosed any such compound nor provided any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research.

However, the claims at issue in *Rochester* are very different from those pending in the instant application, and therefore the reasoning of *Rochester* is not directly applicable to the present case. The claims in *Rochester* were directed to methods comprising administration of specific compound with a specific activity, i.e. selectively inhibiting PGHS-2 activity. The specification did not disclose any compound with this activity, but merely methods that could be used to make such a compound. The court held that the written description requirement was not

satisfied because significant trial-and-error research would be required, including a screening step, in order to identify those compounds with the desired activity.

In contrast, the claims in the instant application are directed to methods of synthesizing one or more compounds through combinatorial biosynthesis. The presently pending claims do not recite the synthesis of any particular compound nor do they recite that any of the synthesized compounds must have any particular activity, e.g., the selective inhibition of PGHS-2 activity as in *Rochester*. As the *Rochester* court stated: "Tellingly,... what the plaintiff's experts' [sic] do not say is that one of skill in the art would, from reading the patent, understand what compound or compounds – which, as the patent makes clear, are necessary to practice the claimed method – would be suitable, nor would one know how to find such a compound except through trial and error." *See Rochester* at 1894 (emphasis added).

In the present case, no particular compound or compounds necessary to practice the claimed invention are recited. That is because no particular compound or compounds are necessary to practice the claimed invention as recited. In fact, such a recitation would undermine important aspects of the present application, which is directed generally towards combinatorial methods useful in the synthesis of "one or more" compounds. One skilled in the art will be aware of known activities and/or features that may be included in a synthesized compound or compounds, will be able to choose which of these activities and/or features he or she wishes to include in the synthesized compound or compounds, and will be able to use the methods recited in the currently pending claims to achieve synthesis of those compound or compounds.

The screening step omitted in *Rochester* was a necessary step in the identification and isolation of a recited compound that exhibits a specific activity, i.e. selectively inhibiting PGHS-2 activity. Here, no such particular compound is necessary to practice the claimed inventions. Thus, the reasoning behind *Rochester* is not directly applicable.

Rejections of Claims 1-3 and 5-23 under 35 U.S.C. § 112, First Paragraph for Lack of Enablement

Pending claims 1-3 and 5-23 stand rejected for lack of enablement. In particular, the Examiner takes the position that Applicant has not provided any examples, and that as a result, a person of ordinary skill in the art would not know how to practice the claimed invention to provide a "useful" result with undue experimentation. This rejection is respectfully traversed;

reconsideration and withdrawal is requested.

The Examiner has listed the non-limiting *Wands* enablement factors and has addressed these factors as they relate to the claimed invention. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of one of ordinary skill in the art;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The existence of working examples; and
8. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Applicant responds to the Examiner's characterization of these factors as they relate to the claimed invention in the order presented by the Examiner.

(1-2) The breadth of the claims and nature of the invention:

As above, the Examiner contends that Applicant provides no structural limitations for the starter units, handles and solid supports used in conjunction with the claimed methods; that the claimed biosynthetic enzymatic machinery includes an unknown number of enzymes and/or enzymatic machinery system constituents; and that no limitations are provided for the synthetic organic chemistry that is further used to diversity the biosynthetic products. Applicant hereby reiterates all the arguments made above in the Number of Methods/Number of Compounds section of the Written Description response, rebutting the Examiner's assertions on each of these points.

For the reasons explained above, Applicant is not claiming "virtually an infinite number of methods for producing virtually an infinite number of compounds", as suggested by the Examiner. As such, in contrast to the Examiner's assertion, the invention has in fact been defined with particularity and the nature of the invention can be determined (and in fact practiced) by those of ordinary skill in the art.

(3 and 5) The state of the prior art and the level of predictability in the art:

The Examiner asserts that the level of predictability in the art is low or absent since there

are no examples of "solid phase" combinatorial biosynthesis.

The Examiner contends that a person of ordinary skill in the art would not know how to pick solid support and/or handles that would ensure a reaction between the biosynthetic enzymatic machinery system and the starter units. In support of this, the Examiner asserts that it is extremely difficult to find an enzyme with activity towards a particular substrate due to the high substrate specificity exhibited by most natural enzymes. Applicant submits that it is well with the knowledge and skill of one of ordinary skill in the art to determine whether a particular enzyme has such stringent specificity such that it will not recognize the particular starter unit that *the practitioner has himself or herself chosen.* That is, the practitioner is not operating in a vacuum. By choosing a desired starter unit or units, one of ordinary skill in the art would know which enzyme or enzymes may use those particular starter units as catalytic substrates. For example, see page 7, lines 20-32, describing well known desirable enzyme/substrate combinations that can be used.

The Examiner concedes that the prior art shows that, in some cases, the biosynthetic enzymatic machinery has relaxed specificity and thus could accommodate a wide array of substrates. One of ordinary skill in the art is presumed to be aware of these examples. However, the Examiner contends that the prior art does not show that the enzymes could accommodate substrates on a solid support, such as a bead or a chip. The Examiner poses the question: "How would a support bound starter unit get transferred from one enzyme to the next in the modular biosynthetic enzymatic machinery when it is bound to a reaction bead?" The simple answer is that the starter unit will be transferred in the same manner as other substrates subjected to modular biosynthetic enzymatic machinery, whether bound to a solid support or not: the enzyme machinery will associate with the substrate, act on it, and then dissociate, leaving the modified substrate free for another enzymatic reaction.

Finally, as described above, Applicant has disclosed that researchers have made various modifications to certain preferred biosynthetic enzymes that alter their catalytic properties, indicating that those skilled in the art are not only able to generally identify the substrate specificity of a given biosynthetic enzymatic machinery system, but are in fact able to specifically engineer variants of these enzymes with altered substrate specificity (see page 6, lines 8-19).

Thus, far from being an unpredictable field, as the Examiner asserts, specific examples of

combinatorial biosynthesis are well known to those of ordinary skill in the art. Using known examples of specific enzyme/substrate combinations, as well as known functionalization reactions, one of ordinary skill in the art is enabled to practice the claimed invention.

(4) The level of one of ordinary skill:

Applicant agrees with the Examiner that the skill level of one of ordinary skill in the art would be high, most likely at the Ph.D. level.

(6 and 7) The amount of direction provided by the inventor and the existence of working examples:

As above, the Examiner contends that Applicant provides no working examples of the claimed methods.

For reasons largely identical to those given above in the Working Examples section of the Written Description response, Applicant submits that the specification does in fact provide adequate enablement support. As indicated above, the description provided must be read from the point of view of one skilled in the art. *See In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996). Those of ordinary skill in the art are well versed in appropriate enzyme/substrate combinations, particularly those specific biosynthetic enzymatic machinery systems recited in claim 1. Furthermore, those of ordinary skill in the art are capable of identifying those functionalization reactions that are appropriate for any given product produced by the enzymatic reaction. As discussed above, it is well established that the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and is available to the public. *In re Buchner* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Thus, when read from the point of view of one of ordinary skill in the art (i.e., with commensurate knowledge of enzyme/substrate combinations and functionalization reactions), Applicant submits that the guidance required by the enablement requirement is provided in the disclosure of novel methods of synthesizing compounds using both enzymatic reactions and organic chemistry.

The Examiner further asserts that the specification does not disclose various reagents and products that are *essential* for the claimed methods.

As an initial matter, Applicant submits that the specification does disclose various

reagents and products that *may be used* with the claimed methods. For example, various enzyme/substrate combinations that may be used in accordance with the presently claimed invention are disclosed on page 7, lines 20-32. Additionally, various functionalization reactions that may be used in accordance with the presently claimed invention are disclosed on page 14, lines 14-27.

However, more importantly, Applicant submits that the Examiner has not appreciated the novelty and utility of the claimed methods since none of these disclosed reagents and/or products are in fact *essential* for practicing the claimed methods, but are merely examples of reagents and/or products that may be used to achieve the synthesis of "one or more compounds", as recited in claim 1. As discussed above, one of ordinary skill in the art will be aware of and will be able to choose appropriate reagents (e.g., starter units, handles and enzymes) that may be useful in producing a desired product(s) in accordance with the methods recited in the currently pending claims. Thus, Applicant submits that one of ordinary skill in the art is in fact enabled to practice the claimed invention based on the teaching of the present disclosure.

(8) The quantify of experimentation needed to make or use the invention based on the content of the disclosure

The Examiner contends that as a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the quantity of experimentation needed to make and/or use the invention would be great. The Examiner relies primarily on the fact that Applicant has not provided any working examples and on the assertion that the art is highly unpredictable.

For the reasons presented above in the Working examples section of the Written Description response, Applicant disagrees. As indicated, the description provided must be read from the point of view of one skilled in the art. *See In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996). Those of ordinary skill in the art are well versed in appropriate enzyme/substrate combinations, particularly those specific enzymes recited in claim 1. Furthermore, those of ordinary skill in the art are capable of identifying those functionalization reactions that are appropriate for any given product produced by the enzymatic reaction.

Disclosure of working examples of techniques known to those skilled in the art is not necessary. *See, e.g., Manual of Patent Examination Procedure*, ch. 2164.05(a), discussing this

issue in the context of enablement. *See also In re Buchner* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and is available to the public.")

Furthermore, in contrast to the Examiner's assertion, Applicant disagrees that the art is highly unpredictable. The quantity of experimentation needed to make or use the invention, based on the content of the disclosure, is neither excessive nor outside the skill set of one skilled in the art. As stated in *Wands*, "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" *Wands* at 1404 (emphasis added). As discussed above, one of ordinary skill in the art is well versed in both appropriate enzyme/substrate combinations, particularly those specific enzymes recited in claim 1, and in appropriate functionalization reactions. The fact that the practitioner may need to perform routine experiments to determine which enzymes and/or functionalization reactions to utilize when practicing the claimed invention does not mean that the art is highly unpredictable. As such, a rejection of the claimed methods based on lack of enablement is improper.

Rejections of Claim 7 under 35 U.S.C. § 112, First Paragraph for Lack of Written Description/New Matter

The Examiner asserts that removal of the phrase "chemically robust" from pending claim 7, which formerly recited "chemically robust handles", constitutes addition of new matter since the amended claim may potentially read on both chemically robust and chemically non-robust handles. Without addressing what, exactly, the amended claim may or may not read on, Applicant submits that removal of the phrase "chemically robust" from pending claim 7 does not constitute new matter. On page 8, lines 17-19 of the originally filed specification, Applicant teaches, "particularly robust functionalities such as aklynes, olefins and iodoalkenes, are particularly preferred, although the method of the present invention is not limited to these functionalities." The Examiner seems to be saying that the Applicant is limited to claiming preferred embodiments described in the originally specification. However, this is not the law. Applicant disagrees with the Examiner's position and requests withdrawal of this ground of

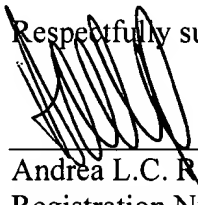
rejection.

In light of the foregoing Remarks and Amendments, Applicant respectfully submits that the present case is in condition for allowance. A Notice to that effect is thus respectfully requested.

If, at any time, it appears that a phone discussion would be helpful or if questions arise regarding the amendments proposed above, please do not hesitate to contact the undersigned at (617) 248-5175.

Please charge any fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,



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